Application Reviews by RFA/Genomics/GC1R-06708

REVIEW REPORT FOR CIRM RFA 12-06R GENOMICS CENTERS OF EXCELLENCE AWARDS (R)

GC1R-06708: CIRM Genomics Center of Excellence

GWG Overall Center Recommendation: Tier 1
GWG Overall Final Score: 82

GWG Data Center Recommendation: Tier 2
GWG Data Center Final Score: 71

CIRM Staff Recommendation: Do not fund

Public Abstract (provided by applicant)
The proposed Genomics Center of Excellence will provide critical genomics and computational support to California stem cell investigators with the highest quality collaborative environment for cutting-edge, data-intensive genomics research. The Center builds upon the strong foundation of our existing BioSequencing Core resource located in the CIRM sponsored Major Facility. By leveraging our existing BioSequencing Core and other cores such as Bio-Engineering, Flow Cytometry, Proteomics, Metabolomics, Molecular Screening, Microscopy, FDA GMP compliant hESC & iPSC Derivation Labs and Banks, and our proven successful track record of collaborative stem cell research, we will provide an invaluable resource for California stem cell Investigators to advance the human stem cell field and stem cell biology genomics research, drive the development of genomics technology and techniques, and deepen our understanding of human disease, with a focus on translating basic research discoveries to the development of novel stem cell based therapeutics. The goals will be achieved through a coordinated approach that integrates: 1) extensive genomics based research collaborations, 2) next generation sequencing, 3) application of advanced bioinformatics analyses and interface with other leaders in the field such as ENCODE and the NIH Epigenome Project, 4) a proven genomics track-record and 5) our documented ability to identify and fund innovative stem cell research.

Statement of Benefit to California (provided by applicant)
The proposed Genomics Center of Excellence will provide critical genomics and computational support to California stem cell investigators with the highest quality collaborative environment for cutting-edge, data-intensive genomics research. The Center builds upon the strong foundation of our existing BioSequencing Core resource located in the CIRM sponsored Major Facility. By leveraging our existing BioSequencing Core and other cores such as Bio-Engineering, Flow Cytometry, Proteomics, Metabolomics, Molecular Screening, Microscopy, hESC & iPSC Derivation Labs and Banks, and our proven successful track record of collaborative stem cell research, we will provide an invaluable resource for California stem cell investigators to advance the human stem cell field and stem cell biology genomics research, drive the development of genomics technology and techniques, and deepen our understanding of human disease, with a focus on translating basic research discoveries to the development of novel stem cell based therapeutics. The goals will be achieved through a coordinated approach that integrates: 1) extensive genomics based research collaborations, 2) next generation sequencing, 3) application of advanced bioinformatics analyses and interface with other leaders in the field such as ENCODE and the NIH Epigenome Project, 4) a proven genomics track-record and 5) our documented ability to identify and fund innovative stem cell research.

Review Summary
This proposal is to establish a CIRM Genomics Center of Excellence that will involve a set of core laboratories at a major California university. There are four Center-initiated projects with induced pluripotent stem cells (iPSCs) as the main focus, although cell derivation from human embryonic stem cells (hESCs) and analysis of normal human tissue will be used extensively as controls. Two of the projects will focus on "disease in a dish models" of early neurological spectrum disorders, while the other two projects will study barriers in iPSC programming with cell populations of interest. All of the center-initiated projects will have a central reliance on a systems-biology approach for the analysis of extensive functional genomic data on relevant cells and cell populations. The collaborative-project program builds on past experience by the applicant's institutional stem cell research center and includes a major educational component as well as outreach to potential collaborators and monitoring of collaborative projects. Quantitative requirements and IT support for large data will be outsourced to local and national organizations.

Center Organization and Operational Plan

- Reviewers agreed that the proposed organizational structure is straightforward and includes an Advisory Board and Collaborative Research Committee, both populated with experienced and well respected scientists from the applicant institution.

- Reviewers expressed concern that important details of the center governance and management such policies for resolving conflicts between center investigators were not included.

- A particular strength of the application is the pre-existing set of core laboratories covering relevant biological, genomic and computational aspects of the research program.

- While reviewers acknowledged that it could be an advantage for the CIRM-funded center to tap into an already flourishing and strong local genomics center, some expressed concern that it might function primarily as an enhancement of the existing center rather than constituting a distinct and focused Stem Cell Genomics Center of Excellence.

- A specific financial commitment from the applicant institution toward support of the proposed Center was not apparent.

- The proposal lacked a discussion of alternative strategies for reallocation of resources should the initial plan require revisions or face any unforeseen conflicts.

Collaborative Research Projects

- Reviewers were impressed by the proposed collaborative project activities and noted that the proposal provides all the essential elements for a strong collaborative research program including educational outreach, workshops, review process and technical expertise with core labs.

- Plans to provide three types of collaborative projects of varying scale were considered well conceived and likely to be responsive to the needs of the stem cell research community.

- Some reviewers were concerned that proposed outreach activities would not be adequate.

CIP-1

This project is based on the hypothesis that a diverse group of single effect mutations will reveal convergent phenotypes that are relevant to the understanding of the more frequent sporadic forms of ASD. The PI will profile the transcriptomes of a large number of iPSC lines from patients with single gene disorders that predispose them to ASD and will use bioinformatics approaches to develop a coherent transcriptional network picture for developing neurons derived from these iPSCs.

- The project is largely exploratory, and the approach lacks innovation.

- While there was a general agreement that only a minority of ASD cases have well-defined genomic causes, reviewers were divided as to whether the proposed approach would reveal a common pathway for ASD symptoms.

- Some reviewers believed that the quantitative analysis required for this project is likely to be beyond the scope and capacity of the investigators.

- Although reviewers generally agreed that the project goals are feasible, there was concern about the lack of some important experimental details and about deficiencies in the chosen cellular models (e.g. cell lines from Fragile X syndrome patients).

- The project features very strong leadership and a team with specific and relevant experience as it relates to this project.

CIP-2

This Project follows up on studies previously completed using a mouse model. Experiments will involve a time-course study to map any changes in transcription and the epigenome that take place during reprogramming in human cells. The aim is to gain a better understanding of cellular reprogramming and discover ways to increase efficiency in the derivation of human iPSCs

- Reviewers differed in their opinions about the project's significance; some felt that the proposed analysis could improve the quality of

reprogrammed cells for use in research and therapy, while others questioned whether the information generated in the study is necessary for successful translation of iPSCs into the clinic.

- The focus on enhancer elements and their functional roles was considered innovative.

- Some reviewers thought that results of the study would be quite limited, as the observed pathways will be dependent on secondary factors such as the methodologies used for reprogramming and specific cell culture platforms, among others.

- Some reviewers suggested that more pressing limitations, such as malignant transformation of reprogrammed cells and strategies for more efficient differentiation of iPSCs into target cells, should be addressed first.

- Significant concerns were raised that failure to identify any meaningful reprogramming intermediates would render the subsequent aims irrelevant.

- There were concerns that the proposed approach may overreach current abilities to draw any meaningful conclusions from the immense number of molecular changes taking place in cells undergoing reprogramming.

- The project leader is a well-accomplished investigator in pluripotent stem cell biology and epigenetics. The research team is extremely capable and appropriate.

CIP-3
This Project examines the basis for the failure to generate authentic hematopoietic stem cells (HSCs) from pluripotent cell populations in vitro. The investigators will define gene expression and epigenetic patterns of HSC populations during in vivo development and compare these patterns with those of cells undergoing differentiation to hematopoietic lineages in vitro.

- Reviewers were highly enthusiastic about the potential significance of this project. They all agreed that understanding the basic biology of HSC differentiation and the ability to recapitulate self-renewal in HSCs would solve a major problem in the field.

- The approach is logical and benefits from careful attention to normal HSC development and subsequent behavior.

- The experiments appear to be highly feasible.

- Reviewers expressed some concerns about the source of cells for in vitro differentiation and the culture methods used to induce differentiation.

- Reviewers cautioned that the functional experiments may only provide meaningful results if a single transcription factor corrects the HSC dysfunction in vitro. Additionally, the experiments will not account for any deficit that may be due to the culture environment.

- An excellent investigator leads the project, and the research team is particularly strong.

CIP-4
This project aims to generate a roadmap of gene expression changes during neuronal development from iPSCs in vitro. The focus will be on RNA diversity and how it might affect intellectual impairment phenotypes in a number of neurodevelopmental disorders.
- Reviewers agreed that any contribution to the molecular pathogenesis of neurodevelopmental disorders would be of high significance; however, they were extremely unenthusiastic about this project and particularly concerned by the lack of a robust rationale.

- The proposed experiments focus mostly on gabaergic neurons, a neuronal type which is not relevant to the indication under study.

- Reviewers raised concerns that the data presented for the RNA editing is based on only a single cell line.

- The project features a strong team with expertise in pluripotent stem cell biology, computational biology and bioinformatics of RNA. Reviewers noted that the research team would benefit from more expertise in neurobiology and neural development.

A motion was made to remove this center-initiated project and requested funds from the application. The motion carried unanimously.

Data Coordination and Management
- This center will build largely on the existing infrastructure at the applicant institution.

-The proposed structure appears to have ample human and computational resources to meet the needs of the center.

- Although the PD and Co-PD were recognized as seasoned investigators in the field, some reviewers questioned whether they had adequate experience in managing projects at the scale required of the stem cell center and were particularly concerned about the lack of expertise in managing, curating and analyzing large human whole genome datasets.

- Concern was expressed about the center's heavy reliance on outside service providers for hardware and software access.

- The proposed staffing and budget for data management appeared appropriate.

Conflicts

- Bradley Bernstein
- Richard Gibbs
- Aarno Palotie
- Barry Rosen
